REMARKS

In response to the Office Action mailed July 25, 2006, Applicants amended claims 1-5, canceled claims 10 and 23-27, and added new claims 28-30. Support for the amendments and the new claims can be found throughout the specification and the claims as originally filed. For example, support for amended claim 15 is found at least at page 33, line 21, through page 34, line 9. Amendments to the specification are to add sequence identifiers and to correct typographical errors. No new matter has been added. Claims 1-9, 11-22 and 28-30 are presented for examination.

The paper copy of the enclosed substitute sequence listing is identical to the computer-readable form, also enclosed.

Priority

Applicants have amended the priority claim to specify that priority application no. 09/244,984 is now US Patent No. 6,842,704. It is presumed that Examiner's comment that application no. 09/244,984 "is not US Patent No. 6,842,704" (emphasis added) was meant to be read as the application "is now US Patent No. 6,842,704." See Office Action at page 3, paragraph 7 (emphasis added).

Information Disclosure Statement

Applicants submit herewith a Supplemental Information Disclosure Statement that specifies the publication date of the references previously submitted but not considered by the Examiner. The references are not included, as they were previously provided in U.S. Application No. 09/244,984, filed February 9, 1999, now U.S. Patent No. 6,842,704. Copies of the references can be provided if required. Applicants ask that the Examiner return an initialed copy of the enclosed form PTO-1449 indicating that he has considered these references.

Sequence Compliance

A substitute sequence listing is enclosed, which is identical to the sequence listing submitted August 27, 2004, in related application U.S. 10/057,321, filed September 24, 2001 (now abandoned). The sequences of SEQ ID NOs:7 and 8 of the enclosed sequence listing were initially disclosed in Black *et al., Nature* 325:729-733 (1997), which is incorporated by reference in the application. See Specification at page 10, line 29, through page 11, line 4. The enclosed sequence listing and the above amendment is believed to satisfy the sequence listing requirements.

35 U.S.C. § 112, second paragraph

Claims 2-7, 11, 12, and 14 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the invention.

Claims 2-4 were amended to correct antecedent basis. The Examiner further states that the meanings of the terms "TACE catalytic domain" and "the pro and catalytic domains of TACE" should be clarified. The structure of the TACE polypeptide is described in the specification at least at page 2, lines 4-9, and page 11, lines 22-24. The pro and catalytic domains are also known and described in the prior art (see, *e.g.*, Black *et al.* (1997), and Moss *et al.* (1997), cited at least at page 2, lines 1-4, of the specification, and cited in the IDS submitted July 27, 2004). The meanings of the terms are clear.

Claims 4 and 5 have been amended to include sequence identifiers.

The term "suitable" has been deleted from claim 6.

The Examiner states that the recitation of TCD molecules in claims 11 and 12 lacks antecedent basis. Applicants disagree. TCD (the TACE catalytic domain) is described at least at page 2, lines 6-7, and is well known in the art. A crystal having a unit cell comprising four crystallographically independent TCD molecules is also described in the specification in Example 2 at pages 33-34. In view of the disclosure in the specification and the knowledge in the art, the meaning of TCD molecules is clear and has proper antecedent basis in the claims.

Claim 14 has been amended to delete reference to "characterized by" and "substantial part thereof."

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 2-7, 11, 12, and 14 under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 112, first paragraph

Written Description. Claims 1-22 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner states that "[g]iven the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention." Office Action at page 9. Claim 10 has been canceled and therefore the rejection of this claim is moot.

Applicants do not concede that the claims fail to satisfy the written description requirement. However, to expedite prosecution, claims 1 and 22 have been amended to specify that the crystal of the polypeptide is of monoclinic space group $P2_1$. The "Trilateral Project WM4: Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims" (hereafter, "the Trilateral Report") (2002) states that claims to a crystalline form of a polypeptide satisfy the written description requirement if the structure of the polypeptide is provided. Trilateral Report at page 67. See also Case 4 of the Trilateral Report at page 66. Since the structure of the polypeptide is provided, claim 1 (and claims 2-9 and 11-14, which depend from claim 1) and claim 22 satisfy the written description requirement.

The Examiner states that "the specification discloses only a single representative species of crystallization buffers that resulted in a TACE crystal that was suitable for x-ray diffraction..." Office Action at page 8. Applicants note that claim 15 does not require that the method produce a TACE crystal suitable for x-ray diffraction, only that the method produce a crystallized TACE polypeptide. Claim 15 has been amended to specify that the crystallization

buffer comprises sodium citrate. Example 2, at pages 33-34 of the specification, describes three buffers (Buffer B, C, and D), which were successfully used to crystallize TACE polypeptide. All three of these buffers contain sodium citrate. In view of the disclosure in the specification regarding buffers used to successfully crystallize a TACE polypeptide, claim 15 (and claims 16-21, which depend from claim 15) also satisfies the written description requirement.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection of claims 1-9 and 11-22 under 35 U.S.C. § 112, first paragraph, for failure to satisfy the written description requirement.

Enablement. Claims 1-22 were rejected under 35 U.S.C. § 112, first paragraph, because "the specification, while being enabling for a crystal of a purified TACE protein as disclosed in Black et al. (1997)...does not reasonably provide enablement for all crystals, TACE polypeptides, TACE binding partners, and methods of crystallization as broadly encompassed by the claims." Office Action at pages 9-10. Claim 10 has been canceled and therefore the rejection of this claim is moot.

Applicants do not concede that the claims are not enabled. However, to expedite prosecution, claims 1 and 22 have been amended to specify that the crystal of the polypeptide is of monoclinic space group $P2_1$. The Trilateral Report states that claims to a crystalline form of a polypeptide satisfy the enablement requirement if the specification teaches how to make the claimed crystals, and if one skilled in the art could use the claimed polypeptide crystal to make the active form of the polypeptide and use it without undue experimentation. Trilateral Report at page 67. See also Case 4 of the Trilateral Report at page 66. The specification discloses how to make the claimed composition at pages 33-34, and one of skill in the art could use the claimed crystal to make the active form of the polypeptide and use it without undue experimentation. In view of the disclosure in the specification, claim 1 (and claims 2-9 and 11-14, which depend from claim 1) and claim 22 satisfy the enablement requirement.

The Examiner states at page 10 that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. Office Action at page 10. The

Examiner further discusses the Wands factors that he believes to be most relevant to the instant rejection. Id. at page 10-15. Applicants address each of these factors below in response to the Examiner's comments.

Breadth of the claims. The Examiner states that the "broad scope of the claimed crystals and crystallization methods is not commensurate with the enablement provided by the disclosure." Id. at page 11. As amended, claim 1 (and the claims depending from claim 1) and claim 22 are limited to compositions comprising a polypeptide in crystalline form, wherein the polypeptide is a TACE polypeptide, and wherein the crystal is of monoclinic space group $P2_1$. As amended, claim 15 (and the claims depending from claim 15) is limited to a method for crystallizing a TACE polypeptide comprising, *inter alia*, mixing a solution comprising TACE polypeptide and a binding partner with a crystallization buffer comprising sodium citrate. The subject matter covered by the claims is no broader than Applicants' contribution.

State of the prior art; level of one of ordinary skill; and level of predictability in the art. The Examiner states that the state of the art at the time of the invention acknowledges a high level of unpredictability for making a protein crystal with an expectation that the crystal will be of diffraction quality. Id. Applicants disclosure describes and indeed demonstrates how to make a composition comprising crystalline TACE, wherein the crystal is of monoclinic space group $P2_1$. The disclosure also describes and demonstrates methods for crystallizing TACE polypeptide using crystallization buffers that comprise sodium citrate. The claims do not require that the crystals be of diffraction quality. Applicants agree that the relevant art is generally unpredictable. However, the present application discloses sufficient information to allow one of ordinary skill in the art to successfully make and use the subject matter covered by the claims.

Amount of direction provided by the inventor; existence of working examples. The Examiner states that the specification only provides a single working example of a crystal and method for making, and the specification fails to provide guidance for other polypeptides as encompassed by the claims with an expectation of obtaining diffraction-quality crystals. Id. at page 13. The claims are not limited to diffraction quality crystals, and Applicants demonstrate the use of three different buffers (Buffers B, C, and D) to generate TACE crystals. See

Specification at page 33, line 21, through page 34, line 9. The disclosure in the specification, including the working example, provides sufficient guidance for one of skill in the art to make and use crystals of TACE polypeptides.

The quantity of experimentation needed to make or use the invention based on the content of the disclosures. The Examiner states that "[w]hile methods of protein crystallization were known at the time of the invention, it was not routine in the art to screen all polypeptides having a substantial number of variations and modifications as encompassed by the claims..." Id. at page 14. The application teaches how to make and use crystals of TACE polypeptides. In view of the disclosure of the specification and the knowledge in the field of protein crystallography, undue experimentation would not be required to make and use the subject matter covered by the claims.

In conclusion, Applicants reiterate that the Trilateral Report, describing the policy of the USPTO regarding protein 3D structure related claims, states that claims to a crystalline form of a polypeptide satisfy the enablement requirement if the specification teaches how to make the claimed crystals, and if one skilled in the art could use the claimed polypeptide crystal to make the active form of the polypeptide and use it without undue experimentation. Trilateral Report at page 67. See also Case 4 of the Trilateral Report at page 66. As described above, Applicants have satisfied the requirements for enablement according to the USPTO guidelines. In view of the disclosure in the specification and the knowledge in the art, claim 1 (and claims 2-9 and 11-14, which depend from claim 1) and claim 22 satisfy the enablement requirement. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 1-9 and 11-22 under 35 U.S.C. § 112, first paragraph, for failure to satisfy the enablement requirement.

Applicants believe the application is in condition for allowance, which action is requested.

Attached is a Petition for Extension of Time for two months, and a check for $450 for the required fee. Please apply any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 16163-039004.

Respectfully submitted,

Date: December 14, 2006

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